I wasn't too serious about the microbes! Thank you for your interesting welcome. CHA.

Reprinted without change of pagination from the
Proceedings of the Royal Society, B, *volume* 139, p. 313, 1952

Lederberg

Leeuwenhoek Lecture

The place of viruses in nature

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(*Delivered* 13 *December* 1951—*Received* 22 *December* 1951)

In the first Leeuwenhoek lecture last year, Sir Paul Fildes (1951) reviewed the history of microbiology. In this, the second lecture, it seems to me appropriate to take stock of our knowledge of one part of the field of microbiology, a part which is full of implications for all branches of biology. There are, as you know, very diverse views as to the nature of viruses. As you will soon discover it anyhow, I may as well confess at the outset that I believe them to be small organisms. In maintaining this, I shall derive considerable moral support from this portrait of Antony van Leeuwenhoek at my side. He was the discoverer of the little animals whose study to-day comprises the field of microbiology. I do not think he would be surprised at the existence of creatures smaller and still smaller, made visible nowadays only by means of electron-microscopy.

I propose to discuss the place in nature of viruses from two points of view, which I will call the taxonomic and the ecological. First, are they animal or vegetable (or neither), and if organisms, where do they fit in in relation to other organisms? Secondly, what is their role in the interaction of one form of life with another form and with environment? I shall subsequently consider the taxonomic and ecological aspects together, in the hope of visualizing the position of viruses in the scheme of things in a way which makes some sort of sense.

Taxonomic approach

The biochemist who sets to work at his bench with relatively pure preparations of a virus, finds that viruses all contain nucleo-proteins. In some plant viruses he can find nothing but nucleo-protein; he compares what he finds with the other materials with which he is familiar, talks of virus-macromolecules and tends to think of them as chemical entities. Approaching viruses from the opposite standpoint, the pathologist finds that viruses are agents of disease, behaving like other small parasites, and he naturally thinks of them as such. I think everyone will admit that viruses behave like parasitic entities, have, in most instances, an autonomous existence and are subject to the action of natural selection. The point of dispute will be as to their origin, whether endogenous or otherwise; and unless new viruses are still being created, their origin may be a matter impossible to settle with certainty.

I should like to put forward six reasons for regarding viruses as organisms. Objections may be raised on points of detail to any one of them, but as a set of facts taken together, they seem to me quite convincing.

(1) *Viruses multiply.* We need, before accepting this as a convincing fact in itself, to know more about the mechanism of this multiplication. If we add a little trypsin to a lot of trypsinogen, we end up with a lot of trypsin; but this is not a good analogy for the type of replication we are now interested in. The suggestion was at one time put forward that cells contained a lot of virus-precursor, only awaiting a suitable stimulus to be turned into virus. The existence of a hundred or so different bacterial viruses capable of multiplying in a dysentery bacillus makes this view difficult to believe. The nature of virus multiplication will be discussed in more detail later.

(2) *Viruses vary.* In fact, they are often hard to keep in a stable state. Their variability is daily taken advantage of, when we try to adapt a virus which attacks one species of host and to make it infect another. Virus variation seems altogether analogous to the mutations of larger organisms; in fact, mutation-rates can be calculated for bacterial viruses and for the so-called O-D change of Influenza A virus. The possibility of applying genetical techniques with profit to viruses makes it hard to regard them as anything but living things.

(3) *Viruses are chemically complex.* Like living things generally, they contain nucleo-proteins, with nucleic acids sometimes of the ribose, sometimes of the desoxyribose type. The animal pathogenic viruses are all more complex than this; vaccinia virus for instance contains also carbohydrate, lipoid, copper, biotin, riboflavin and several distinct proteins. Even the plant viruses, in which only nucleo-protein is demonstrable, cannot be regarded as homogeneous molecules. They may have a uniform composition by the chemists' crude tests; they may be crystallized or exist as fibrous crystals in particles of the same length and breadth; but the more delicate biological tests for activity and for presence or absence of variants show that they are not uniform.

(4) *Viruses are normally antigenic* in the host they attack. That is, they act, not as bits of the host's own protein would be expected to do, but as something foreign,

'not self'. Burnet & Fenner (1950) have discussed how at the basis of immunological reactions lies the ability of the antibody-forming mechanisms to distinguish between things 'self' and 'not self', producing antibodies only to the latter. There are, as is well known, exceptions. Lens-protein can stimulate antibody production in the same species. So can nervous and other tissues, especially when combined with adjuvants. There are also virus infections which fail to give rise to demonstrable antibodies. That of lymphocytic choriomeningitis may fail to do so in latently infected mice, though it does in guinea-pigs. Bittner's virus which causes mammary cancer in mice does not produce antibodies in mice. Nor does the grey-lung virus of mice which Glover and I described (Andrewes & Glover, 1945) give rise to demonstrable active immunity or antibody. I emphasize these exceptions to make it clear that the 'six reasons' are not infallible laws, and also (as I shall discuss later) to show that absence of antibody formation in a condition does not prove that a virus is not concerned.

(5) *Virus gradient.* It will, I think, be admitted by all that the larger viruses are organisms. As one proceeds down the scale to the smaller ones, there is at no point a sharp break either in size or other properties, at least amongst animal viruses, suggesting that the smaller ones may be something of different nature altogether. The bacterial viruses differ amongst themselves in size but over quite a small range compared with animal viruses. Concerning plant viruses it is harder to generalize, for so very few of the vast numbers known can be transmitted under conditions permitting their properties to be determined.

(6) *Parasitic habits.* The ability of viruses to produce transmissible disease, as do larger parasites, is a property so obvious as to require no emphasis. What is less generally appreciated is that, again like larger parasites, there is even more often a latent infection. The existence of this may be only discoverable by indirect means, as by passing infected tissue to a susceptible or 'indicator' organism; or it may be made manifest by some jolt or shock which disturbs a host-parasite equilibrium.

Alternatives to the organismal theory

As I see it, the old idea that viruses are something on the borderline between the living and dead is no longer worth discussion. For the chief alternative to the view that viruses are organisms seems to be that they are something like a gene or plasmogene which has reached a new and happier environment or has broken the bonds of discipline within its own environment and gone ahead on an autonomous existence. Such an agent can hardly be considered 'dead' by any definition. I have already indicated reasons for refusing to admit that the term virus molecule or macro-molecule is appropriate for a virus. The crystallization of a plant virus was certainly a shock to virologists, but now that they have had a little time to recover, it does not seem so revolutionary as it did at first that virus particles can arrange themselves neatly in two- or three-dimensional patterns. What is much more difficult is Bernal & Fankuchen's (1937) demonstration by X-ray analysis that the atoms and molecules within such a crystal or pure crystal are so regularly oriented one to another that metabolic activity on their part is hardly conceivable. I shall hope to show later that this difficulty is not insuperable.

Virus-like agents

Those who are reluctant to accept the view that viruses are organisms are wont to point to transmissible agents having a certain similarity to them in properties, and to suggest that there is a whole class of things acting much like organisms and yet of fundamentally different nature. Murphy (1932) coined the term 'transmissible mutagens' for these. I will briefly discuss two examples. Pneumococci can exist in a complete virulent form manufacturing a type-specific carbohydrate or in an avirulent degraded form lacking this carbohydrate. Type-specific strains produce an agent capable of changing the type of these degraded forms. Thus a degraded Type II pneumococcus may be converted by means of a Type III transforming factor into a fully type-specific organism, not Type II like its ancestors but of Type III. Moreover, as such, it will produce not only specific Type III polysaccharide but more transforming factor capable of continuing to make more converts of more avirulent Type II. The transforming factor is a polymerized desoxyribose nucleic acid (Avery, MacLeod & McCarty 1944). Here is something fundamental to the understanding of genetic mechanisms. We need not, however, conclude, as some writers do, that the transforming agent is akin to a virus. True, it multiplies or is multiplied. But there is no evidence that it varies; it is chemically simpler than any virus, containing no protein; and it certainly does not act like a parasite, in the way viruses do. We may perhaps hope that knowledge about it may help to teach us what tricks a bacterial virus uses to deviate the host-cells' metabolism to its own ends.

Of a very different nature is the killer-substance (paramecin) produced by some strains of the protozoon *Paramecium aurelia* (killer-strains) (Sonneborn 1948). Sensitive strains of the animal exposed to cultures of killer strains are killed apparently by as little as one particle of paramecin. This paramecin is formed by or from a particulate agent called kappa in the cytoplasm of killer paramecia, and under appropriate conditions kappa particles can pass over to normal paramecia and convert them also into killers by virtue of continuing to produce more kappa. The killing substance paramecin seems to be very similar in properties to kappa, containing nucleo-protein and being particulate, but in some respects it differs. There is a genetic aspect of the whole thing, for kappa can only multiply in cells of a particular genetic constitution. Some years ago several biologists drew attention to this phenomenon as a cytoplasmic mechanism simulating the action of a virus; kappa, it was contended, was of the nature of a plasmagene under the control of a nuclear gene, hereditarily transmitted in the cytoplasm and producing a substance having lethal effects on 'indicator organisms'. It seems fair to urge that the virus-like agent in pneumococci differs demonstrably from a virus and is not a virus; kappa also falls out of the category of betwixt-and-between agents, but on opposite grounds; there seems no good reason for not calling it a symbiotic organism. Kappa can be stained and its population within a cell enumerated; it contains protein and desoxyribose-nucleic acid; it is if anything rather too large to be called a virus. If you call nitrogen-mustard a chemotherapeutic agent, you may say that infected paramecia can be cured by chemotherapy. Those who have worked upon it for

years from the point of view of genetics (Sonneborn 1948; Beale 1951) are now disposed (rather reluctantly, I fancy) to concede that all the facts are consistent with the view that kappa is an organism. They still, however, suggest 'the question of whether it should be considered a plasmagene or a parasite...is perhaps academic' (Sonneborn), or ask 'is the distinction a real one or merely formal' (Beale). I should think that any organism with a soul of its own, even a micro-organism with a micro-soul, would take it very much amiss if anyone suggested that such a fundamental matter were 'academic' or 'merely formal'.

There may be, there probably are, instances like those I have quoted, but in which it is still more difficult to be sure whether certain facts are best explained by the presence of a parasite or in some other way. They are mostly phenomena but little understood, and so far the more we understand them the easier it is to conclude 'here is a parasite' or 'here is something else'. It is when we cannot focus clearly that black and white are apt to look like grey.

What kind of organism?

I hope that I have carried you with me far enough to have successfully inculcated some bias towards the organismal view of viruses. In any event we have next to consider what sort of organisms, if organisms they are, viruses must be. Are they animal or vegetable? Are they small bacteria or something quite different?

The two alternatives were first posed by Green (1935). 'Viruses', he writes, 'may be surviving parasitic forms developed from free-living ultramicrobes formerly inhabiting the earth and now extinct'. Or 'they may be parasitic forms of life developing by retrograde evolution from visible microbes similar to visible forms now existent'. He strongly favours the second possibility, partly on the grounds that we know of no free-living non-parasitic forms of the dimensions of viruses and says 'all life smaller than a certain size is obligately dependent upon life of a greater magnitude than that size'. My late chief, P. P. Laidlaw, in his Rede Lecture (1938), ably supported the view that viruses are descended from larger parasites, losing, as so many specialized parasites do, one structure, one function after another. 'Parasites', he wrote, 'may through indolence give up making substances which are always at hand in the host's cells'; and he traced how the smallest viruses might have evolved from larger parasites, till (in a memorable phrase) they only 'lived a borrowed life, truly the supreme summit of parasitism'. This view, often called the Green-Laidlaw hypothesis, will be so familiar to you that I need not elaborate it further. Let us rather consider whether the knowledge which has accrued since 1938 makes it easier or harder to believe in derivation of viruses from larger parasites.

The bacterium-virus borderline

There have been suggestions that some viruses might be derived from protozoa. There is an obscure little protozoon called Toxoplasma which inhabits cells in the central nervous system of various species, including man. Some maintain that there are analogies between it and the rabies virus. But most people would rather study the possible derivation of viruses from bacteria. It is only too certain that

whatever may be the case at the lower end of the scale we do not know how to draw a sharp line between bacteria and viruses at the top end. There are two definite groups standing between acknowledged bacteria and typical viruses and very difficult to place; these are the rickettsiae and the large group of viruses related to that of psittacosis. One can employ as criteria—morphology, formation of inclusion bodies, intra- or extracellular mode of growth, transmission by arthropods, susceptibility to chemotherapy; none of these is satisfactory in helping us to draw a line between the bacteria and the viruses. Some of the smaller viruses are pretty close to those of the psittacosis group; some of these again are very like rickettsiae; and these in turn come close to some small bacteria such as that of tularaemia. Even chemotherapy is no good guide. There have lately turned up in our laboratories two viruses which are susceptible to aureomycin and terramycin but otherwise stand apart from the psittacosis group; these are the grey-lung virus of mice (Andrewes & Glover 1945) and a virus causing hepatitis in mice (Gledhill & Andrewes 1951).

We can only conclude that taxonomy is made for man, not vice versa (a truth often forgotten), that all taxonomic distinctions are somewhat artificial, and that the dividing line between small bacteria and large viruses is not an easy one to draw. So far then a derivation of viruses from bacteria seems not improbable.

Multiplication of viruses

We must, however, look very closely into the mode of multiplication of some of the smaller viruses. And here I come to the most difficult part of my lecture; for knowledge is advancing so rapidly that anything I say may be out of date by to-morrow morning. Most fascinating new findings are being reported all the time, but I find myself in much doubt as to how many of them to believe.

Unexpected things have been discovered lately about the morphology of influenza and related viruses. Several workers had noted in addition to the well-known spherical forms, some short filaments. In 1949, Chu, Dawson & Elford found that recently isolated influenza viruses existed predominantly in the form of long filaments; there were suggestions that spheres formed within these filaments or by fragmentation of them.

Disappearance of viruses

One thing about virus multiplication seems clear. In very many instances virus introduced to a susceptible cell 'disappears' for a matter of minutes in the case of bacterial viruses or of hours or days with animal viruses. In effect, one cannot recover within the latent period before multiplication begins, any virus which will infect another cell. The most favoured and the most attractive hypothesis is that the virus has passed into a phase of its life cycle, in which infectivity is lacking. Bauer (1949) was one of the first to suggest this. In the case of influenza, Hoyle (1950) has found that before infectivity reappears there is an increase in the small complement-fixing antigen—so-called soluble antigen; later appears something capable of causing agglutination of fowl and mammalian red cells (a property also of the complete virus particle), and finally new infective virus particles themselves.

Hoyle believes that the soluble antigen is one phase in the virus's life cycle, but Fulton (1949) disputes that this is proven.

A decision is not possible at present as to the existence of a 'soluble' phase in the life cycle, or at any rate a phase of breakdown into smaller units. We may expect electron microscopy to resolve the dilemma before long. In fact, it is already indicating that a smaller phase may be concerned in the multiplication of one of the larger typical viruses, that of molluscum contagiosum of man. Here it seems that the earliest stages of virus multiplication involve the production of fine granular material composed of particles about 100 mμ across. Progressively larger particles appear later, culminating in a crop of elementary bodies having nearly four times that diameter (Rake & Blank 1950).

Multiplication of bacterial viruses (phages)

We may hope for light to be shed soon from the study of bacterial viruses. We know in the case of some of them that in the latent period the phage disappears. Breaking up the bacterial cell by various means fails to reveal even the original particle in an infective form. This 'eclipse' stage lasts half-way through the cycle. Studies with tagged atoms indicate that the protein and desoxyribosenucleic acid of the phage particles come from the medium in which growth is occurring rather than from bacterial constituents. Optical studies suggest a disruption of bacterial chromatin at an early stage. Apparently the infecting virus seizes a key position and organizes the bacterial metabolism to its own ends. Luria (1950) calls it 'parasitism at the genetic level'. In effect, the bacterial virus is a pirate, who, having single-handed obtained command of the bridge of the captured ship, forces all hands to do his will.

Much has been learnt by study of phage mutation and recombination. Mutant phage particles occur spontaneously, differing from the original type either in host range or in the appearance of the plaques they produce on agar plates or in other ways. When a single bacterium is infected with two variants of phage A, each carrying different marker characters, say B and C respectively, the resulting crop of particles will consist of some like the originals AB and AC, but others like the wild type AA or containing both variant characters B and C together. This phenomenon, genetic recombination, is perhaps an early, simple forerunner of bisexual multiplication. In any case its study by Luria and others on genetic lines has proved very profitable. Luria believes that a large phage may contain as many as 100 genetic units capable of recombination. He at one time suggested that a bacterial virus broke up, after entering the cell, into very many subunits which replicated independently and then re-formed to make new phage particles. Recent work by his colleague Dulbecco has, I gather, made this theory untenable. It would, indeed, be hard to believe that the individuality of an organism was highly subdivided and that the separate bits pursued an independent existence for a time, including in their experiences a certain amount of shuffling, and finally, a new deal, which reconstituted a number of similar or rather different individual viruses. It is easier to imagine that the identity of the virus as a whole is not lost, though

it may in course of multiplication exchange genetic material with other particles in its neighbourhood.

We must beware of visualizing what happens solely in terms of protein chemistry, remembering that the larger bacterial viruses consist of heads with some internal structure and of tails also somewhat complex. There is here, however, a zone where the boundary between chemistry and morphology is not so very wide.

Other equally able students of bacterial viruses have elucidated matters by studies of quite a different sort. Lysogenic bacteria are familiar objects of the countryside to all bacteriologists; they are organisms associated symbiotically with a bacterial virus which does not apparently affect them, but the presence of which is revealed by the use of an indicator organism—a bacterium which is sensitive. There are in reality two separate phenomena. In one, the phage-resistant bacteria are constantly throwing out a few sensitive variants, and it is in these that the bacterial viruses multiply and keep going, though the culture as a whole is not visibly affected. In the true lysogenic culture of an organism such as *B. megatherium*, the virus is really symbiotic and divides as the bacterium divides; no free virus is liberated capable of infecting a susceptible indicator. But certain treatments which Lwoff (1950) calls 'shock' disturb the equilibrium between virus and host so that massive lysis of the culture occurs, fully active virus being liberated from every cell in the culture. Ultra-violet radiation is an effective shocking mechanism. Lwoff calls the symbiotic phage 'probacteriophage'; he thinks of it as an immature form of phage which the shock reactivates.

Boyd (1951) found evidence of a similar state of affairs in *Salmonella typhi-murium*, but his evidence suggests that his A 1 phage may exist in one or other of two phases—a symbiotic phase corresponding to Lwoff's prophage and a fully active lytic phase. He declines to regard the symbiotic phase as immature, for immature beings do not commonly propagate indefinitely.

Common to all the work I have mentioned is the idea that a virus may exist in a phase or stage incapable of being demonstrated by the usual techniques but able to be converted into the better known state. This phase may be a normal or, at times, an abnormal phenomenon.

The idea of an incomplete virus is seen in the results of several workers with influenza. Von Magnus (1951) found that if fertile hens' eggs were infected allantoically with a large excess of influenza virus, a product appeared which had the same power as influenza virus of agglutinating vertebrate red cells but was much less infective; it had, moreover, a smaller diameter than the ordinary virus. He suggests that in too heavily infected cells, virus multiplication may begin, but that some essential ingredient may be used up, so that the virus produced is imperfect.

Stuart-Harris (1939) obtained a variant of influenza virus having an affinity for the nervous system and ability to kill mice on intracerebral injection. This multiplies regularly in mouse brains, while ordinary strains of influenza do not. Schlesinger (1950), however, obtained evidence suggesting partial multiplication of the latter so that haemagglutinin and complement-fixing antigen increased, though infectivity did not. He also felt that an incomplete virus was being

produced. The neurotropic variant presumably differs from other influenza viruses in being able to continue multiplying progressively in mouse brain.

Burnet & Lind (1951) also used the neurotropic variant of influenza virus in recombination experiments analogous to those described with bacterial viruses; Burnet (1951*a*) reported these to this Society in his Croonian lecture of 1950 and more fully in his Herter lectures in America (1951*b*). Briefly they used two markers, the property of neurotropism and the antigenic pattern of the viruses. Non-neurotropic swine influenza virus was introduced into mouse brains with a suitable dose of neurotropic virus of the WS antigenic make-up, and by ingenious manipulations viruses were obtained having neurotropic properties combined with the antigenic characters of swine influenza. They interpreted this finding as a recombination of genetic elements of two viruses, and this may well be so, though in my view other explanations have not been excluded.

All this is very reminiscent of some work done in 1937 by Berry & Dedrick (1936). They studied two serologically related viruses affecting rabbits, the highly fatal myxoma and the benign non-lethal infectious fibroma. By injecting living fibroma virus along with heated myxoma, they obtained an active strain resembling the fatal myxoma, or others of properties intermediate between the two. At the time, gene recombinations had not been heard of in relation to viruses and comparisons were made with Griffith's type transformations of pneumococci. Possibly, similar mechanisms are concerned in all these things; we should then think of transforming factors as equivalent to the genes which the pneumococci, the myxoma virus, the phages and influenza viruses barter with one another, and not as of the same status as the viruses themselves.

Virus nomenclature

There is currently a good deal of argument as to whether it is appropriate to apply the Linnaean binomial system of nomenclature to viruses (Andrewes 1951). Very few animal virologists think the time ripe to apply a comprehensive system to the animal viruses, for we do not sufficiently understand how to group them. Plant virologists seem very evenly divided as to the wisdom of attempting this immediately in their field. I know of virtually no students of bacterial viruses who would consider such a classification suitable for bacteriophages. But although a comprehensive, ambitious, rigid nomenclature may not be appropriate as yet, the matter needs earnest study, and it is possible that by detailed attention to a few better-known groups, the principles most usefully applicable to viruses can be worked out.

Consider for a moment something really basic for virus taxonomy. If viruses are derived from and akin to bacteria, they are plants and can be considered as an order, perhaps to be called Virales as Breed, Murray & Hitchens (1944) suggest. It may be, however, that further study of their mode of multiplication will suggest that they stemmed independently from a primitive form of life and must be placed somewhere remote from bacteria; then they will constitute a separate kingdom, requiring perhaps a separate code of nomenclature. They would set 'Twenty Questions' a pretty problem, for they would be neither vegetable, animal or

mineral nor abstract. It is not only from the point of view of taxonomy that we need to know if the multiplication of viruses is of a nature apart from that of bacteria. The conceptions of pro-phage, incomplete virus and symbiotic virus which have cropped up are at the basis of much of what I now want to say in my ecological approach.

Ecological approach

Viruses, acting as parasites, have a clear role to play in the balance of nature amongst the agents controlling larger living things. Some have doubtless been causing similar diseases for a long time; Burnet has pointed out that mumps is much as it was in the time of Hippocrates, 2500 years ago—not that that is very long in the eyes of a student of evolution. A virus with many similar properties, influenza, is, on the other hand, always changing. Mumps and man have reached an equilibrium on the basis of an endemic, rarely fatal, infection, mostly of children. But many viruses reach an equilibrium on an altogether different plane. The most successful parasites are those which do not kill their host and perish with it, but those which affect it not too brutally and make adequate arrangements for transfer to a fresh host. 'Parasitism', in Theobald Smith's words (1934), 'is a compromise or truce between two living things' and this compromise often leads to a condition of latent infection. He conceives, by the way, that 'very minute parasites exist, but owing to their constant presence or invisibility they cannot be differentiated from the other contents of the cell-body'.

But the truce is usually an uneasy one, accompanied, to quote Theobald Smith again, 'by predatory processes whenever opportunity is offered one or the other party'. This opportunity I have elsewhere referred to as a 'jolt' which upsets a virus-host equilibrium and leads to emergence of a virus disease, appearing as it were from nowhere. As this idea of an upset balance is of such importance for understanding odd results in the virus field, I make no apology for giving, briefly, a few examples.

Latent infection of budgerigars with psittacosis may be activated by overcrowding or bad husbandry (Meyer 1942). Mice latently infected with lymphocytic choriomeningitis virus may develop symptoms if broth is injected intracerebrally (Traub 1939). Herpes simplex (fever blisters) in man blossoms forth under various jolting stimuli such as fever, ultra-violet light or eating cheese. Lwoff's (1950) ultra-violet shock has already been mentioned as an activator of phage.

We can thus never argue that an apparently new virus is an example of latter-day Creation unless we have looked rather carefully beneath the surface of things.

Now a virus, to be a successful parasite, needs to be able to multiply in its host, to have some means of getting from one host to another and, if this travel is likely to be prolonged, to be tough enough to survive the journey. The means for getting from one host to another may involve getting a ride in an arthropod vector, or even multiplication in that vector—a very good way of ensuring safe arrival at the journey's end; or dispersal may be by excreta from the respiratory, intestinal or urinary tracts, through the air or in food or drink or mechanically. The attainment

of a state of equilibrium as a latent infection will ensure survival in the original host, but might very well militate against free dispersal of virus into the environment. It seems likely that some viruses have evolved another mechanism of dispersal altogether, not to the neighbours of their host but to his offspring. Whether or not viruses can be handed down to the next generation in the germplasm is not proven, but it seems very likely. I will mention some suggestive examples. The virus of St Louis encephalitis can be transmitted transovarially from one generation to the next in a bird-mite, *Dermanyssus gallinae*; hence it can get to the infected bird, and a mosquito may intrude into the mite-bird cycle and carry the virus off to produce an infection in man; but it seems likely that the heritable mite infection is at the basis of the virus's story (Smith, Blattner & Heys 1946). The garden tiger moth, *Arctia caja*, can be bred in captivity for two or three generations with ease; after that a fatal virus infection is apt to appear. This is apparently transmitted through egg or sperm. In some such instances the larva must at times be infected before birth, for it may go down with the disease as early as two days after hatching (Smith, K. M. 1951). The jolt which activates a latent infection is presumably concerned with the unfavourable circumstances of close confinement, but its action is here prolonged over some months and two or three generations, rather a wearing-down than a jolting effect. A disease of sheep in Scotland, 'scrapie', is characterized by violent itching, so that sheep rub off their wool against fences (Greig 1940). After inoculation the incubation period may be as long as two years. Scottish farmers know of 'scrapie rams'; the lambs which they beget are likely to succumb to scrapie, often after two years, though the ewes which bear them may remain well. The disease seems to be carried in the sperm; and the same is thought to be true of fowl paralysis.

There is another method of perpetuation of virus, half-way between the hereditary and the infective. A virus carried by the mother may be able to infect newborn offspring. Thus Bittner's mammary cancer virus of mice is transferred in the milk. The mouse hepatitis virus which Gledhill and I (Gledhill & Andrewes 1951) are now studying seems to get across to sucklings but not to older mice. Recent work by Gross (1951) suggests that in mouse leukaemia an agent may be able to infect mice aged 1 day but not those of 2 days or older.

Viruses and cancer

We have considered how viruses may have undergone retrograde evolution till they have lost almost everything; some seem to have gone further than the rest in losing the mechanism of getting out and about, their passports for travel to a new host. It may well be that virus of such a sort is concerned with causation of cancer. We would have to suppose, on this line of thought, that virus in a perfectly harmless equilibrium with a cell is subjected to a jolting stimulus such as application of a carcinogenic chemical or physical agent. Maybe a mutation either of virus or cell or both is concerned, and the virus gets out of hand stimulating cells to multiply and thus to increase many-fold in its own turn. On a short-term basis, the virus has won a great victory; but it is a Pyrrhic victory and in the end gets it nowhere, for its host dies and the virus with it. The forces of evolution have

directed it into a blind alley; but in the maze of evolution there are more blind alleys than arterial roads.

This conception is not pure fantasy; it is illustrated by Shope's rabbit papilloma and the carcinomas which derive from it. The papilloma virus will produce warts with fair regularity in the natural host, the cotton-tail rabbit, and these are serially transmissible; it is a naturally occurring, self-limited disease. In the domestic rabbit the virus also produces warts, but their serial transmission is difficult, often impossible. Nevertheless, virus is still present in these warts and will immunize rabbits when suspensions are injected intraperitoneally. Eventually the domestic rabbit warts commonly become malignant, and the carcinomas thus caused have been serially transplanted in other rabbits. Virus is still not demonstrable as a rule by transmission experiments, any more than in other mammalian cancers. But its presence can be revealed indirectly, for antibodies to the papilloma virus appear in the sera of tumour-bearing rabbits, Kidd & Rous (1940). After some years' propagation, however, even this evidence for the presence of a virus has been lost. Those, and their name is legion, who do not care for the virus theory of cancer, acclaim this as proof that the virus merely started off the cancers and is not their continuing cause. I cannot contradict them; but to me it seems equally or more probable that the virus has attained a new state of equilibrium with the cells, still stimulating them to multiply abnormally, but no longer being produced and liberated in excess so as to be able to cause visible antibody production or else not doing so because it has lost the necessary reacting antigen. We may have had before our eyes the evolution of a typical non-filterable mammalian cancer from a typical transmissible virus disease.

Vegetative and reproductive aspects of virus growth

Can we by putting together our taxonomic and ecological glimpses of viruses attain a binocular vision allowing us to see them in better perspective? I suggest that many things may look a little different if we consider that the real virus is the entity multiplying vegetatively within its host cell. The early stages of its life history we have not been able to visualize by any optical or electron-optical means. It seems to be non-transmissible at that stage to other hosts. It may be present in forms smaller than those we normally recognize. It may be multiplying diffusely within the cell and recombining later, not remaining always in compact packets as bacteria do; as yet, however, the evidence for such an extreme revolutionary view is rather tenuous.

At the end of a certain cycle of multiplication, there appear the virus forms which are familiar to us—the bacterial viruses with their heads and tails, the elementary bodies of the poxes, the spheres of influenza. These are things we can see with optical devices, we can manipulate and transmit to fresh hosts, after making studies of their chemical composition and other properties. Such a thing we call 'the Virus', even though it is an inert object, devoid of practically all metabolic activity. I suggest that we might as well call a poppy-seed 'the Poppy', describe the species *Papaver phloeas* on the basis of seed characters, and ignore the roots, the stems and the leaves. There are, of course, certain differences; the tiny but

tough poppy-seed, which carries on the line of poppies by being blown by the wind to fertile soil, is something far smaller than the vegetative phase of the plant. The vegetative phase of a virus is not likely to be larger than the inert virus particle; further work may show that it is considerably smaller. It is not a prophage or a pro-virus, or a virus precursor, but an essential stage in the virus's life cycle which is normally but not always followed by development of the more familiar virus form.

This conception does I feel help to resolve certain difficulties: we need no longer feel so worried about the inertness of virus particles; and particularly we can appreciate better what happens when a virus adopts the hereditary instead of the infective method of getting into new hosts. It simply abandons for the time, as do many higher plants, the reproductive part of its life cycle. We are all familiar with mosses in which fructification rarely occurs; a common representative is a species of *Plagiothecium* which forms nice whitish green cushions in beech-woods. Such a plant forms capsules only under exceptional circumstances. A virus adopting such a policy would lose, perhaps permanently, the properties permitting its transmission by inoculation, becoming what I have earlier called a 'toothless virus'. Its morphology is likely to differ from our preconceived notions, and it may not be microscopically demonstrated till we know better what to look for.

All this suggests that one course which virus evolution may follow is an integration of virus with its host which becomes closer and closer until ultimately no jolt is capable of disrupting it. It has even been suggested by Wilson Smith and others that in the completeness of the union some genetic interchange may take place between parasite and host, the host thus acquiring fresh material on which the forces of evolution may play for its ultimate benefit. It is, I suppose, imagined that the host genes admit a little foreign brother to sit upon the chromosome bench beside them. I should anticipate that geneticists might be as reluctant to accept the notion that a virus can become a gene as pathologists are to admit a transformation in the opposite direction.

What may be a true or a spurious example of species formation under the influence of a virus is afforded in the bacterial genus *Salmonella*. Species of new antigenic constitution have been described, though they may be in fact nothing but old species in which particular antigens have been suppressed by a symbiotic phage.

Everything seems to suggest that a stable virus-host cell equilibrium is one end-result of contact between a virus and its victim. Many instances of apparently new diseases are readily explained by upset of the balance when stability is not fully established. By looking at the virus particle as the equivalent of the poppy-seed, we seem to escape from some of the difficulties which beset the subject; but we do well to keep our ideas flexible while so much more is being learnt every day about the mechanism of virus multiplication. It seems, in any case, that the viruses can be readily placed within the scheme of existing biological knowledge without doing great violence to any part of it. I make this point because some writers have lately adopted a different view. In a recent review of a book, in *Nature*, standing over the initials C.D.D., we read of 'an audience which does not yet realize that

the old foundations of botany, zoology and microbiology are being undermined and that the classical notions of evolution, species, individual, sexual reproduction, organism, disease and life are disintegrating under their eyes'. A little sweeping! To allay any possible panic amongst Fellows of the Society, I take my stand on the opinion that there is at any rate nothing established by modern work on viruses which need lead to fear of such comprehensive disintegration.

The place of viruses in taxonomy will become clear before long. Their place in ecology, however, is never static. Viruses get out of their natural hosts, infect strange ones, perhaps find everything in their favour, and so produce epidemics of disease. Then they settle down to an equilibrium, either endemic disease with occasional flurries of greater activity or, at a lower level, reach a state of closer and closer union, culminating in the blissful surrender of perfect symbiosis.

References

Andrewes, C. H. 1951 *Acta path. microbiol. scand.* **28**, 211.
Andrewes, C. H. & Glover, R. E. 1945 *Brit. J. Exp. Path.* **26**, 379.
Avery, O. T., Macleod, C. M. & McCarty, M. 1944 *J. Exp. Med.* **79**, 137.
Bauer, D. J. 1949 *Nature, Lond.*, **164**, 767.
Beale, G. H. 1951 *Nature, Lond.*, **167**, 256.
Bernal, J. D. & Fankuchen, I. 1937 *Nature, Lond.*, **139**, 923.
Berry, G. P. & Dedrick, H. M. 1936 *J. Bact.* **31**, 50.
Boyd, J. S. K. 1951 *J. Path. Bact.* **63**, 445.
Breed, R. E., Murray, E. G. & Hitchens, P. 1944 *J. Bact.* **47**, 421.
Burnet, F. M. 1951*a* *Proc. Roy. Soc.* B, **138**, 47.
Burnet, F. M. 1951*b* *Johns Hopk. Hosp. Bull.* **88**, 119.
Burnet, F. M. & Fenner, F. 1950 *Production of antibodies*, 2nd ed. London: Macmillan.
Burnet, F. M. & Lind, P. 1951 *J. Gen. Microbiol.* **5**, 59, 67.
Chu, C. M., Dawson, I. M. & Elford, W. J. 1949 *Lancet*, **1**, 602.
Fildes, P. 1951 *Proc. Roy. Soc.* B, **138**, 65.
Fulton, F. 1949 *Nature, Lond.*, **164**, 189.
Gledhill, A. W. & Andrewes, C. H. 1951 *Brit. J. Exp. Path.* **32**, 559.
Green, R. G. 1935 *Science*, **82**, 443.
Greig, R. 1940 *Trans. Highl. Agric. Soc. Scot.* (5), **52**, 71.
Gross, L. 1951 *Proc. Soc. Exp. Biol., N.Y.*, **76**, 27.
Hoyle, L. 1950 *J. Hygiene*, **48**, 277.
Kidd, J. G. & Rous, P. 1940 *J. Exp. Med.* **71**, 813.
Laidlaw, P. P. 1938 *The Rede Lecture*. Cambridge University Press.
Luria, S. E. 1950 *Viruses* 1950. Calif. Inst. Technol., Pasadena, California.
Lwoff, A., Siminovitch, L. & Kjeldgaard, N. 1950 *Ann. Inst. Pasteur*, **79**, 815.
Meyer, K. F. 1942 *Medicine*, **21**, 175.
Murphy, J. B., Sturm, E., Favilli, G., Hoffman, D. C. & Claude, A. 1932 *J. Exp. Med.* **56**, 117.
Rake, G. & Blank, H. 1950 *J. Invest. Dermatol.* **15**, 81.
Schlesinger, B. W. 1950 *Proc. Soc. Exp. Biol., N.Y.*, **74**, 541.
Smith, K. M. 1951 Personal communication.
Smith, M. G., Blattner, R. J. & Heys, F. M. 1946 *J. Exp. Med.* **84**, 1.
Smith, T. 1934 *Parasitism and disease*. Princeton University Press.
Sonneborn, T. M. 1948 *Proc. Nat. Acad. Sci., Wash.*, **34**, 413.
Stuart-Harris, C. H. 1939 *Lancet*, **1**, 497.
Traub, E. 1939 *J. Exp. Med.* **69**, 801.
Von Magnus, P. 1951 *Acta path. microbiol. scand.* **28**, 278.

PRINTED IN GREAT BRITAIN AT THE UNIVERSITY PRESS, CAMBRIDGE
(BROOKE CRUTCHLEY, UNIVERSITY PRINTER)